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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BONDINELL, William, E. [US/US]; 1512 Franklin Lane, Wayne, PA 19087 (US). NEEB, Michael, J. [US/US]; 414 Bill Smith Boulevard, King of Prussia, PA 19406 (US).

(74) Agents: STEIN–FERNANDEZ, Nora et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406–0939 (US).

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(57) Abstract

This invention relates to substituted heterocyclic compounds which are modulators, agonists or antagonists, of the CCR5 receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5, including, but no limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, by the use of substituted heterocyclic compounds which are CCR5 receptor antagonists. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co–receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

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COMPOUNDS AND METHODS

FIELD OF THE INVENTION

This invention relates to substituted heterocyclic compounds which are modulators, agonists or antagonists, of the CC chemokine receptor CC-CKR5 now designated as CCR5 (*Nature Medicine* **1996**, *2*, 1174-8). In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

BACKGROUND OF THE INVENTION

T cells are not only key regulators of the immune response to infectious agents but are believed critical for the initiation and maintenance of the inflammatory reaction in a variety of chronic diseases. Increased numbers or enhanced activation state of T cells, especially CD4+ T cells, have been demonstrated in the synovium of individuals with rheumatoid arthritis (M.J. Elliott and R. N. Maini, Int. Arch. Allergy Immunol. 104: 112-1125, 1994), in the bronchial mucosa of asthmatics (C.J. Corrigan and A.B. Kay, Immunol. Today 13:501-506, 1992), in the lesions of multiple sclerosis (R. Martin and H. F. McFarland, Crit. Rev. Clin. Lab. Sci. 32: 121-182, 1995), in psoriatic lesions (J.L. Jones, J. Berth-Jone, A. Fletcher and P.E. Hutchinson, J. Pathol. 174: 77-82, 1994) and in the fatty streaks of atherosclerosis (R. Ross, Annu. Rev. Physiol. 57: 791-804, 1995).

T cells, as well as other inflammatory cells, will migrate into tissues in response to the production of a variety of chemotactic factors. Among these factors are a superfamily of 8-12 kDa proteins known as the chemokines. These proteins share structural features such as the presence of 3-4 conserved cysteine residues. RANTES, which stands for Regulated upon Activation Normal T cell Expressed and Secreted, is an 8 kDa protein member of CC branch of the chemokine family. These proteins recruit and activate immune and inflammatory cells through an interaction with G-protein coupled receptors. The CC branch is defined by the absence of an intervening amino acid residue between the first two cysteine residues and members of this family predominately elicit the migration of mononuclear cells, eosinophils and basophils (M. Baggiolini, B. Dewald, and B. Moser, Adv. Immunol. 55: 97-179, 1994; and J.J. Oppenheim, C.O.C. Zachariae, N. Mukaida, and K. Matsushima, Annu. Rev. Immunol. 9: 617-648, 1991).

RANTES potently produces chemotaxis of T cells, basophils, eosinophils, monocytes and mast cells. RANTES was originally identified as gene product induced late after antigen activation of T-cells (T.J. Schall, J. Jongstra, B.J. Dyer, J. Jorgensen, et al., J. Immunol. 141:1018-1025, 1988), however, RANTES has been shown to be synthesized and secreted by a diverse group of cells that include epithelial and endothelial cells (C. Stellato, L.A. Beck, G.A. Gorgone, D. Proud, et al., J. Immunol. 155: 410-418, 1995; and A. Marfaing-Koka, O. Devergne, G. Gorgone, A. Portier, et al., J. Immunol. 154: 1870-1878, 1994), synovial fibroblasts (P. Rathanaswami, M. Hachicha, M. Sadick, T.J. Schall, et al., J. Biol. Chem. 268: 5834-5839, 1993) and dermal fibroblasts (M. Sticherling, M. Kupper, F. Koltrowitz, E. Bornscheuer, et al., J. Invest. Dermatol. 105: 585-591, 1995), mesangial cells (G. Wolf, S. Aberle, F. Thaiss, et al., Kidney Int. 44: 795-804, 1994) and platelets (Y. Koameyoshi, A. Dorschner, A.I. Mallet, E. Christophers, et al., J. Exp. Med. 176: 587-592, 1992). In these cells RANTES mRNA is rapidly upregulated in response to IL-1 or TNFa. Although RANTES mRNA is not usually detected in normal tissues (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995), increased mRNA or protein has been found in diseases characterized by a mononuclear infiltrate. For example, RANTES mRNA was visualized using *in situ* hybridization in renal allografts undergoing rejection (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995; and K.C. Nadeau, H. Azuma and N.I. Tilney, Proc. Natl. Acad. USA 92: 8729-8733, 1995) in the skin of atopic dermatitis patients after exposure to antigen (S. Ying, L. Taborda-Barata, Q. Meng, M. Humbert, et al., J. Exp. Med. 181: 2153-2159, 1995), and in endothelial cells of coronary arteries undergoing accelerated atherosclerosis after cardiac transplant (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995). Further, increased immunoreactive protein for RANTES has been detected in bronchoalveolar lavage fluid (R. Alam, J. York, M. Boyers, et al., Am. J. Resp. Crit. Care Med. 149: A951, 1994) and sputum from asthmatic individuals (C.M. Gelder, P.S. Thomas, D.H. Yates, I.M. Adcock, et al., Thorax 50: 1033-1037, 1995).

Several receptors have been identified that bind RANTES. In particular, CCR5, when expressed in either HEK 293 cells or CHO cells, binds RANTES. This receptor is expressed in T-cells and in monocytes and macrophages, immune/inflammatory cells which are important in the maintenance of a chronic inflammatory reaction. Pharmacological characterization of CCR5 indicates similarities to the RANTES binding site observed on isolated T cells. Therefore, antagonism of RANTES' action on CCR5, as well as antagonism of other natural

modulators of CCR5, should inhibit the recruitment of T cells into inflammatory lesions and provide a novel therapeutic approach for the treatment of atopic and autoimmune disorders.

Since T cells express CCR5, selective receptor modulators of CCR5, particularly antagonists, are likely to provide beneficial effects in diseases including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

A subset of compounds included in formula (I) have been reported to have 5-$HT_{1D/1B}$ receptor antagonist activity (FR 2758328, published 17 July 1998, and FR 2761069, published 25 September 1998), or tocolytic oxytocin receptor antagonist activity (WO 94/07496, published 14 April 1994, and WO95/25443, published 28 September 1995).

Surprisingly, it has now been discovered that this class of non-peptide compounds, in particular substituted heterocyclic compounds of formula (I), function as CCR5 receptor modulators, and therefore, have utility in the treatment and prevention of disease states mediated by CCR5 receptor mechanisms.

SUMMARY OF THE INVENTION

The present invention is to novel compounds of formula (I) and their novel use as CCR5 modulators for the treatment of certain disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans. The preferred compounds for use as CCR5 modulators are those compounds of Formula (I) as noted herein.

Further, the present invention is directed to methods for making and using the compounds of formula (I), as well as pharmaceutical compositions of formula (I) or a pharmaceutically acceptable salt thereof.

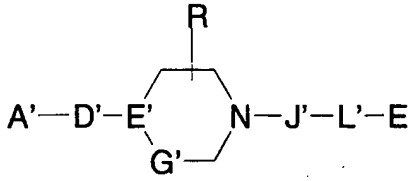
DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted of formula (I) are CCR5 receptor modulators. It has also now been discovered that selective inhibition of CCR5 receptor mechanisms by treatment with the receptor modulators of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for entry into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Compounds of formula (I) for use herein as CCR5 modulators include those compounds as described in FR 2758328, published 17 July 1998, FR 2761069, published 25 September 1998, WO 94/07496, published 14 April 1994, and WO95/25443, published 28 September 1995. Each of these references is incorporated herein in their entirety.

Preferred compounds for use as CCR5 modulators are those compounds of formula (I) as noted herein.

A preferred group of compounds for use herein are those compounds of the formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

in which:

the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl or is optionally present as the N-oxide;

A' is aryl, heteroaryl, or tetrahydronaphthyl, each of which is optionally substituted with one or more of R^1;

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, CH_2CF_3, aryl, aralkyl, $(CH_2)_aNR^2R^3$, $(CH_2)_aNR^2COR^4$, $(CH_2)_aNR^2CO_2R^5$, $(CH_2)_aNR^2SO_2R^6$, $(CH_2)_aCONR^7R^8$, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group),

$(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^9$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, COR^{12}, $CONR^7R^8$, $CONR^7(CH_2)_cOC_{1-4}$alkyl, $CONR^7(CH_2)_aCO_2R^{13}$, $CONHNR^{14}R^{15}$, $CONR^7SO_2R^{16}$, CO_2R^{17}, cyano, trifluoromethyl, NR^2R^3, NR^2COR^4, $NR^{18}CO(CH_2)_aNR^{18}R^{19}$, $NR^{18}CONR^{18}R^{19}$, $NR^2CO_2R^5$, $NR^2SO_2R^6$, $N=CNR^{18}NR^{18}R^{19}$, nitro, hydroxy, C_{1-6}alkoxy, OCF_3, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{20}R^{21}$, SR^{22}, SOR^{23}, SO_2R^{23}, $SO_2NR^{20}R^{21}$ or halogen, or R^1 is a 5- to 7-membered ring containing 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, optionally substituted with hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, (C_{1-6}alkyl)C_{1-6}alkyl, $CONR^7R^8$, CO_2R^{17}, cyano, aryl, trifluoromethyl, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen;

a is 1, 2, 3 or 4;

b is 0, 1, 2 or 3;

c is 1, 2 or 3;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl, or R^2 and R^3 together with the nitrogen to which they are attached, form a 5- to 6-membered heterocyclic ring which ring may be optionally substituted by an oxo group, or, when there are 6 ring members, the ring may optionally contain one oxygen or one sulfur atom;

R^4 is hydrogen, C_{1-6}alkyl or C_{1-4}alkoxyalkyl, or, when R^1 is NR^2COR^4, R^4 is $(CH_2)_{1-3}$ and forms a ring with A';

R^5 is C_{1-6}alkyl;

R^6 is C_{1-6}alkyl or phenyl;

R^7 and R^8 are independently hydrogen or C_{1-6}alkyl, or R^7 and R^8 together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring, wherein when there are 6 ring members, the ring may optionally contain one oxygen or one sulfur atom;

R^9 is C_{1-4}alkyl, optionally substituted by a C_{1-6}alkoxy;

R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^{12} is hydrogen or C_{1-6}alkyl;

R^{13} is hydrogen or C_{1-6}alkyl;

R^{14} and R^{15} are independently hydrogen or C_{1-6}alkyl;

R^{16} is hydrogen or C_{1-6}alkyl;

R^{17} is hydrogen or C_{1-6}alkyl optionally substituted with one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or NR^2R^3;

R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl;

R^{20} and R^{21} are independently hydrogen or C_{1-6}alkyl, or R^{20} and R^{21} together with the nitrogen to which they are attached form a 5- to 6-membered

saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain in the ring one oxygen or one sulfur atom.

R^{22} is hydrogen or C_{1-6}alkyl;

R^{23} is C_{1-6}alkyl;

D' is either a bond or represents $[C(R^{24})_2]_{a'}$, $[C(R^{24})_2]_{a'}CO$, CO, $CO[C(R^{24})_2]_{a'}$, $O[C(R^{24})_2]_{a'}$, $S[C(R^{24})_2]_{a'}$, $O[C(R^{24})_2]_{a'}CO$, $[C(R^{24})_2]_{c'}OCO$, $NR^{25}[C(R^{24})_2]_{a'}$, $NR^{25}[C(R^{24})_2]_{a'}CO$, $[C(R^{24})_2]_{c'}NR^{25}CO$, $NR^{25}CO[C(R^{24})_2]_{a'}$, $NR^{25}SO_2[C(R^{24})_2]_{a'}$, $[C(R^{24})_2]_{c'}NR^{25}SO_2$, $CR^{24}=CR^{24}CO$, $C\equiv CCO$, $(C(R^{24})_2)_{c'}SO_2$, $SO_2[C(R^{24})_2]_{a'}$, $NR^{25}[C(R^{24})_2]_{a'}SO_2$, $NR^{25}SO_2[C(R^{24})_2]_{a'}SO_2$, $O[C(R^{24})_2]_{a'}SO_2$, $SO_2NR^{25}[C(R^{24})_2]_{1-2}$, $[C(R^{24})_2]_{b'}COO[C(R^{24})_2]_2$, $[C(R^{24})_2]_{b'}CONR^{25}[C(R^{24})_2]_{1-2}$; and when E' and G' together are CR^{27}-$C(R^{26})_2$, then D' may further be O, NR^{25}, $CONR^{25}$, SO_2NR^{25}, $OCONR^{25}$, $NR^{25}COO$, $NR^{25}CONR^{25}$, $[C(R^{24})_2]_{a'}NR^{25}[C(R^{24})_2]_{b'}$, $[C(R^{24})_2]_{a'}O[C(R^{24})_2]_{b'}$, $CO[C(R^{24})_2]_{a'}NR^{25}$, $NR^{25}[C(R^{24})_2]_{a'}O$, $NR^{25}[C(R^{24})_2]_{a'}NR^{25}$, $O[C(R^{24})_2)]_{a'}NR^{25}$, $O[C(R^{24})_2]_{a'}O$, $CO[C(R^{24})_2]_{a'}O$, $SO_2[C(R^{24})_2]_{a'}NR^{25}$, $SO_2[C(R^{24})_2]_{a'}O$, $[C(R^{24})_2]_{a'}SO_2NR^{25}$, $[C(R^{24})_2]_{a'}CONR^{25}$, $O[C(R^{24})_2]_{a'}SO_2NR^{25}$, $O[C(R^{24})_2]_{a'}CONR^{25}$, $NR^{25}[C(R^{24})_2]_{a'}SO_2NR^{25}$, $NR^{25}[C(R^{24})_2]_{a'}CONR^{25}$, $NR^{25}CO[C(R^{24})_2]_{a'}NR^{25}$, $NR^{25}SO_2[C(R^{24})_2]_{a'}NR^{25}$, $(C(R^{24})_2)_{a'}S(C(R^{24})_2)_{b'}$, COO, $CR^{24}OH$, $C(R^{24})_{a'}CR^{24}OH$; and when E' and G' together are CR^{27}-$C(R^{26})_2$ or $C=CR^{26}$, D' may further be $CR^{24}=CR^{24}$ or $C\equiv C$; and a' is 1-6, b' is 0-1, c' is 0-2;

R^{24} is hydrogen or C_{1-6}alkyl;

R^{25} is hydrogen or C_{1-6}alkyl;

E' and G' together are $NC(R^{26})_2$, $NC(R^{26})_2C(R^{26})_2$, $CR^{27}C(R^{26})_2$ or $C=CR^{26}$;

R^{26} is hydrogen or C_{1-6}alkyl;

R^{27} is hydrogen, OR^{28}, NHR^{28}, CN, NO_2, R^{28}, SR^{29}, COR^{29}, $CHOHR^{29}$, CO_2R^{29}, $NHCOR^{29}$, $NHCO_2R^{29}$, $NHSO_2R^{29}$, or $OCONHR^{29}$;

R^{28} is hydrogen, C_{1-5}alkyl, aryl or aralkyl;

R^{29} is C_{1-5}alkyl, aryl or aralkyl;

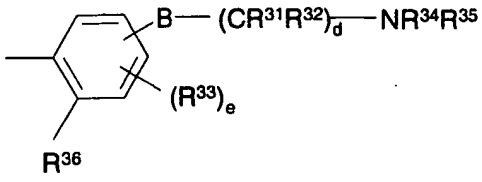
R is one or more of hydrogen or C_{1-6}alkyl, or R is oxo;

J' is CO or SO_2;

L' is NR^{30}, O or $C(R^{30})_2$;

R^{30} is hydrogen or C_{1-6}alkyl;

E represents group (a):



(a);

in which

R^{31} and R^{32} are independently hydrogen or C_{1-6}alkyl;

R^{33} is hydrogen, C_{1-6}alkyl, CO_2R^{37}, $NHCO_2R^{38}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{37} is hydrogen or C_{1-6}alkyl and R^{38} is C_{1-6}alkyl;

d is 1 to 4;

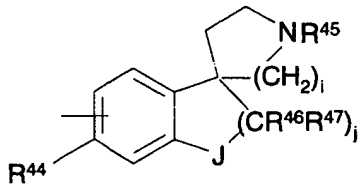
e is 1 or 2;

R^{34} and R^{35} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

B is oxygen, $S(O)_f$, $CR^{39}=CR^{40}$, C=C, or $CR^{39}R^{40}$ wherein R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl, and wherein f is 0, 1 or 2, or B is NR^{41} wherein R^{41} is hydrogen, C_{1-6}alkyl or phenylC_{1-6}alkyl; and

R^{36} is hydrogen or R^{36} taken together with R^{30} forms a group D, wherein D is $(CR^{42}R^{43})_g$, wherein g is 2, 3 or 4, and R^{42} and R^{43} are independently hydrogen or C_{1-6}alkyl, or D is $(CR^{42}R^{43})_h$-G wherein h is 0, 1, 2 or 3, and G is oxygen, sulfur or $CR^{42}=CR^{43}$;

alternatively, E represents group (b):



(b);

in which:

R^{44} is hydrogen or C_{1-6}alkyl, or R^{44} and R^{30} together form a group -K-, wherein K is $(CR^{48}R^{49})_k$, wherein k is 2, 3, or 4, and R^{48} and R^{49} are independently hydrogen or C_{1-6}alkyl, or K is $(CR^{48}R^{49})_l$ –L, wherein l is 0, 1, 2, or 3, and L is oxygen, sulfur or $CR^{48}=CR^{49}$;

R^{45} is hydrogen or C_{1-6}alkyl;

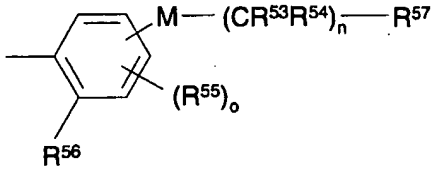
R^{46} and R^{47} are independently hydrogen or C_{1-6}alkyl;

J is oxygen, $CR^{50}R^{51}$, or NR^{52}, wherein R^{50}, R^{51} and R^{52} are independently hydrogen or C_{1-6}alkyl, or J is a group $S(O)_m$ wherein m is 0, 1 or 2;

i is 1, 2 or 3; and

j is 1, 2 or 3;

alternatively, E represents group (c):



(c);

in which:

M is oxygen, $S(O)_p$, $CR^{58}=CR^{59}$, C=C or $CR^{58}R^{59}$, wherein p is 0, 1 or 2, and R^{58} and R^{59} are independently hydrogen or C_{1-6}alkyl, or M is NR^{60} wherein R^{60} is hydrogen or alkyl;

R^{53} and R^{54} are independently hydrogen or C_{1-6}alkyl;

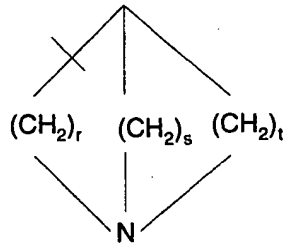
R^{55} is hydrogen, C_{1-6}alkyl, CO_2R^{61}, $NHCO_2R^{62}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{61} is hydrogen or C_{1-6}alkyl, and R^{62} is C_{1-6}alkyl;

R^{56} is hydrogen, or together with R^{30} forms a group –Q-, wherein Q is $CR^{63}=CR^{64}$, $CR^{63}=CR^{64}CR^{63}R^{64}$, or $(CR^{63}R^{64})q$, wherein q is 2 or 3, and R^{63} and R^{64} are independently hydrogen or C_{1-6}alkyl;

n is 0, 1, 2 or 3;

o is 1 or 2; and

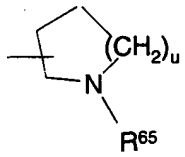
R^{57} is a group of formula (d):



(d)

wherein r, s and t are independently integers having the value 1, 2 or 3;

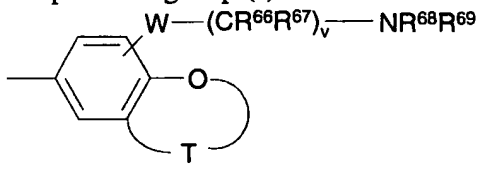
or R^{57} is a group of formula (e), which may be optionally substituted by one or more of C_{1-6}alkyl:



(e)

wherein u is 0,1, 2 or 3 and R^{65} is hydrogen or C_{1-6}alkyl;

alternatively, E represents group (f):



(f);

in which:

R^{66} and R^{67} are independently hydrogen or C_{1-6}alkyl;

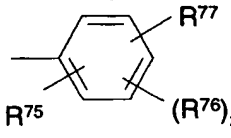
R^{68} and R^{69} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

T is $-(CR^{70}R^{71})_w-$ or $-O(CR^{70}R^{71})_x-$, wherein R^{70} and R^{71} are independently hydrogen or C_{1-6}alkyl, wherein w is 2 or 3, and x is 1, 2 or 3;

v is 1 to 4; and

W is oxygen, $S(O)_y$, wherein y is 0, 1 or 2, or W is NR^{72}, wherein R^{72} is hydrogen or C_{1-6}alkyl, or W is $CR^{73}=CR^{74}$, C=C, or $CR^{73}R^{74}$, wherein R^{73} and R^{74} are independently hydrogen or C_{1-6}alkyl;

alternatively, E represents group (g):



(g);

in which:

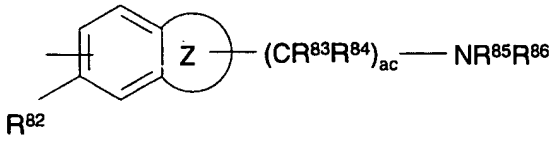
R^{75} is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy, or R^{75} and R^{30} taken together from a group -X-, wherein X is $(CR^{78}R^{79})_{aa}$, wherein aa is 2, 3 or 4, and R^{78} and R^{79} are independently hydrogen or C_{1-6}alkyl, or X is $(CR^{78}R^{79})_{ab}$-Y, wherein ab is 0, 1, 2 or 3, and Y is oxygen, sulfur or $CR^{78}=CR^{79}$;

R^{76} is hydrogen, C_{1-6}alkyl, CO_2R^{80}, $NHCO_2R^{81}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{80} is hydrogen or C_{1-6}alkyl, and R^{81} is C_{1-6}alkyl;

z is 1 or 2; and

R^{77} is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, or R^{77} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom, and optionally, a further heteroatom selected from oxygen, nitrogen or sulfur;

alternatively, E represents group (h):



(h);

in which:

R^{82} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halogen, or R^{82} together with R^{30} form a group -AA-, wherein AA is $(CR^{87}R^{88})$ad, wherein ad is 1, 2 or 3, and R^{87} and R^{88} are independently hydrogen or C_{1-6}alkyl, or AA is $(CR^{87}CR^{88})_{ae}$-AB, wherein ae is 0, 1 or 2, and AB is oxygen, sulfur, $CR^{87}=CR^{88}$, $CR^{87}=N$,

$CR^{87}NR^{88}$ or N=N;

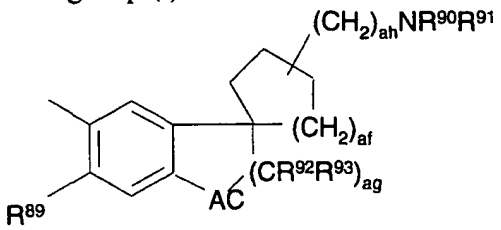
R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl;

R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

ac is 0 to 4; and

Z is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

alternatively, E is group (i):



(i);

in which:

R^{89} is hydrogen or C_{1-6}alkyl or R^{89} and R^{30} together form a group -AD- wherein AD is $(CR^{94}R^{95})$ah wherein ah is 2, 3 or 4 and R^{94} and R^{95} are independently hydrogen or C_{1-6}alkyl or AD is $(CR^{94}R^{95})_{ai}$-AE wherein ai is 0, 1, 2 or 3 and AE is oxygen, sulfur or $CR^{94}=CR^{95}$;

R^{90} and R^{91} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

R^{92} and R^{93} are independently hydrogen or C_{1-6}alkyl;

AC is oxygen, $CR^{96}R^{97}$ or NR^{98} wherein R^{96}, R^{97} and R^{98} are independently hydrogen or C_{1-6}alkyl or AC is a group S(O)aj wherein aj is 0, 1 or 2;

af is 1, 2 or 3;

ag is 1, 2, 3, or 4; and

ah is 0, 1, 2, 3 or 4.

For compounds of formula (I) various embodiments are as follows. It will be understood that the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl or is optionally present as the N-oxide.

Suitably, A' is an aryl ring, a heteroaryl ring, or tetrahydronaphthyl. Suitably A' is optionally substituted by one or more substituents R^1. Preferably A' is an optionally substituted phenyl.

Suitably, R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, CH_2CF_3, aryl, aralkyl, $(CH_2)_aNR^2R^3$, $(CH_2)_aNR^2COR^4$, $(CH_2)_aNR^2CO_2R^5$, $(CH_2)_aNR^2SO_2R^6$, $(CH_2)_aCONR^7R^8$, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^9$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, COR^{12}, $CONR^7R^8$, $CONR^7(CH_2)_cOC_{1-4}$alkyl, $CONR^7(CH_2)_aCO_2R^{13}$, $CONHNR^{14}R^{15}$, $CONR^7SO_2R^{16}$, CO_2R^{17}, cyano, trifluoromethyl, NR^2R^3, NR^2COR^4, $NR^{18}CO(CH_2)_aNR^{18}R^{19}$, $NR^{18}CONR^{18}R^{19}$, $NR^2CO_2R^5$, $NR^2SO_2R^6$, $N=CNR^{18}NR^{18}R^{19}$, nitro, hydroxy, C_{1-6}alkoxy, OCF_3, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{20}R^{21}$, SR^{22}, SOR^{23}, SO_2R^{23}, $SO_2NR^{20}R^{21}$ or halogen, or R^1 is a 5- to 7-membered ring containing 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, optionally substituted with hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, (C_{1-6}alkyl)C_{1-6}alkyl, $CONR^7R^8$, CO_2R^{17}, cyano, aryl, trifluoromethyl, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen.

Suitably, R^2 and R^3 are independently hydrogen or C_{1-6}alkyl, or suitably, R^2 and R^3 together with the nitrogen to which they are attached, form a 5- to 6-membered heterocyclic ring. Suitably, the ring may be optionally substituted by an oxo group, or, when R^2 and R^3 form a 6-membered ring, the ring may optionally contain one oxygen or one sulfur atom. When the ring is a 6-membered ring substituted by an oxygen or sulfur atom, the oxygen or sulfur atom are preferably in the 4-position.

Suitably, R^4 is hydrogen, C_{1-6}alkyl or C_{1-4}alkoxyalkyl, or, when R^1 is NR^2COR^4, R^4 is $(CH_2)_{1-3}$ and forms a ring with A'.

Suitably R_5 is C_{1-6}alkyl.

Suitably, R^6 is C_{1-6}alkyl or phenyl.

Suitably, R^7 and R^8 are independently hydrogen or C_{1-6}alkyl, or suitably, R^7 and R^8 together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring. Suitably, when the ring is 6-membered, the ring may optionally contain one oxygen or one sulfur atom.

Suitably, R^9 is C_{1-4}alkyl, wherein the C_{1-6}alkyl is optionally substituted by a C_{1-6}alkoxy.

Suitably, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl.

Suitably, R^{12} is hydrogen or C_{1-6}alkyl.

Suitably, R^{13} is hydrogen or C_{1-6}alkyl.

Suitably, R^{14} and R^{15} are independently hydrogen or C_{1-6}alkyl.

Suitably, R^{16} is hydrogen or C_{1-6}alkyl.

Suitably, R^{17} is hydrogen or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or NR^2R^3. Preferably, when there is more than one substituent, there are two substituents.

Suitably, R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl.

Suitably, R^{20} and R^{21} are independently hydrogen or C_{1-6}alkyl, or suitably, R^{20} and R^{21} together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom.

Suitably, R^{22} is hydrogen or C_{1-6}alkyl.

Suitably, R^{23} is C_{1-6}alkyl.

Suitably, D' is either a bond or represents $[C(R^{24})_2]_{a'}$, $[C(R^{24})_2]_{a'}CO$, CO, $CO[C(R^{24})_2]_{a'}$, $O[C(R^{24})_2]_{a'}$, $S[C(R^{24})_2]_{a'}$, $O[C(R^{24})_2]_{a'}CO$, $[C(R^{24})_2]_{c'}OCO$, $NR^{25}[C(R^{24})_2]_{a'}$, $NR^{25}[C(R^{24})_2]_{a'}CO$, $[C(R^{24})_2]_{c'}NR^{25}CO$, $NR^{25}CO[C(R^{24})_2]_{a'}$, $NR^{25}SO_2[C(R^{24})_2]_{a'}$, $[C(R^{24})_2]_{c'}NR^{25}SO_2$, $CR^{24}=CR^{24}CO$, $C\equiv CCO$, $(C(R^{24})_2)_{c'}SO_2$, $SO_2[C(R^{24})_2]_{a'}$, $NR^{25}[C(R^{24})_2]_{a'}SO_2$, $NR^{25}SO_2[C(R^{24})_2]_{a'}SO_2$, $O[C(R^{24})_2]_{a'}SO_2$, $SO_2NR^{25}[C(R^{24})_2]_{1-2}$, $[C(R^{24})_2]_{b'}COO[C(R^{24})_2]_2$, $[C(R^{24})_2]_{b'}CONR^{25}[C(R^{24})_2]_{1-2}$; and when E' and G' together are CR^{27}-$C(R^{26})_2$, then D' may further be O, NR^{25}, $CONR^{25}$, SO_2NR^{25}, $OCONR^{25}$, $NR^{25}COO$, $NR^{25}CONR^{25}$, $[C(R^{24})_2]_{a'}NR^{25}[C(R^{24})_2]_{b'}$, $[C(R^{24})_2]_{a'}O[C(R^{24})_2]_{b'}$, $CO[C(R^{24})_2]_{a'}NR^{25}$, $NR^{25}[C(R^{24})_2]_{a'}O$, $NR^{25}[C(R^{24})_2]_{a'}NR^{25}$, $O[C(R^{24})_2)]_{a'}NR^{25}$, $O[C(R^{24})_2]_{a'}O$, $CO[C(R^{24})_2]_{a'}O$, $SO_2[C(R^{24})_2]_{a'}NR^{25}$, $SO_2[C(R^{24})_2]_{a'}O$, $[C(R^{24})_2]_{a'}SO_2NR^{25}$, $[C(R^{24})_2]_{a'}CONR^{25}$, $O[C(R^{24})_2]_{a'}SO_2NR^{25}$, $O[C(R^{24})_2]_{a'}CONR^{25}$, $NR^{25}[C(R^{24})_2]_{a'}SO_2NR^{25}$, $NR^{25}[C(R^{24})_2]_{a'}CONR^{25}$, $NR^{25}CO[C(R^{24})_2]_{a'}NR^{25}$, $NR^{25}SO_2[C(R^{24})_2]_{a'}NR^{25}$, $(C(R^{24})_2)_{a'}S(C(R^{24})_2)_{b'}$, COO, $CR^{24}OH$, $C(R^{24})_{a'}CR^{24}OH$; and when E' and G' together are CR^{27}-$C(R^{26})_2$ or $C=CR^{26}$, D' may further be $CR^{24}=CR^{24}$ or $C\equiv C$; and a' is 1-6, b' is 0-1, c' is 0-2.

Suitably, R^{24} is hydrogen or C_{1-6}alkyl.

Suitably, R^{25} is hydrogen or C_{1-6}alkyl.

Suitably, E' and G' together are $NC(R^{26})_2$, $NC(R^{26})_2C(R^{26})_2$, $CR^{27}C(R^{26})_2$ or $C=CR^{26}$.

Suitably, R^{26} is hydrogen or C_{1-6}alkyl.

Suitably, R^{27} is hydrogen, OR^{28}, NHR^{28}, CN, NO_2, R^{28}, SR^{29}, COR^{29}, $CHOHR^{29}$, CO_2R^{29}, $NHCOR^{29}$, $NHCO_2R^{29}$, $NHSO_2R^{29}$, or $OCONHR^{29}$.

Suitably, R^{28} is hydrogen, C_{1-5}alkyl, aryl or aralkyl.

Suitably, R^{29} is C_{1-5}alkyl, aryl or aralkyl.

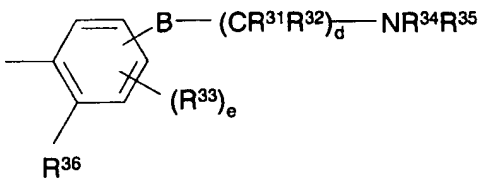
Suitably, R is one or more of hydrogen or C_{1-6}alkyl, or R is oxo.

Suitably, J' is CO or SO_2.

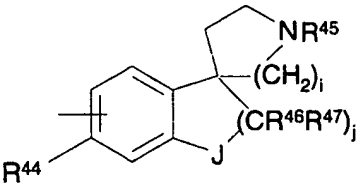
Suitably, L' is NR^{30}, O, or $C(R^{30})_2$.

Suitably, R^{30} is hydrogen or C_{1-6}alkyl.

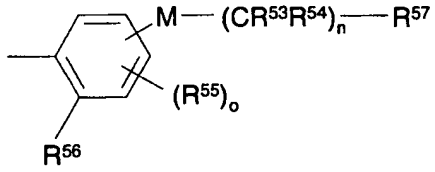
Suitably, substituent E is selected from the following groups:



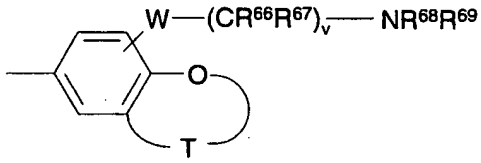
(a);



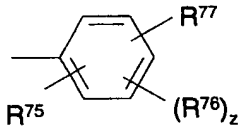
(b);



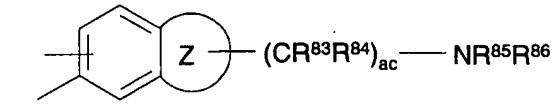
(c);



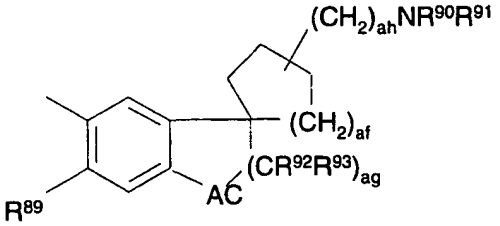
(f);



(g);



(h); and



(i).

Preferably, E is selected from group (a), (b) and (g).

Suitably, when E is group (a), suitably, R^{31} and R^{32} are independently hydrogen or C_{1-6}alkyl; suitably, R^{33} is hydrogen, C_{1-6}alkyl, CO_2R^{37}, $NHCO_2R^{38}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{37} is hydrogen or C_{1-6}alkyl and R^{38} is C_{1-6}alkyl; suitably, R^{34} and R^{35} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur; suitably, B is oxygen, $S(O)_f$, $CR^{39}=CR^{40}$, C=C, or $CR^{39}R^{40}$ wherein R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl, and wherein f is 0,

1 or 2, or B is NR^{41} wherein R^{41} is hydrogen, C_{1-6}alkyl or phenylC_{1-6}alkyl; and suitably, R^{36} is hydrogen or R^{36} taken together with R^{30} forms a group D, wherein D is $(CR^{42}R^{43})_g$, wherein g is 2, 3 or 4, and R^{42} and R^{43} are independently hydrogen or C_{1-6}alkyl, or D is $(CR^{42}R^{43})_h$-G wherein h is 0, 1, 2 or 3, and G is oxygen, sulfur or $CR^{42}=CR^{43}$. Suitably, d is an integer from 1 to 4; and e is an integer from 1 to 2.

Suitably, when E is group (b), suitably, R^{44} is hydrogen or C_{1-6}alkyl, or R^{44} and R^{30} together form a group -K-, wherein K is $(CR^{48}R^{49})_k$, wherein k is 2, 3, or 4, and R^{48} and R^{49} are independently hydrogen or C_{1-6}alkyl, or K is $(CR^{48}R^{49})_l$ –L, wherein l is 0, 1, 2, or 3, and L is oxygen, sulfur or $CR^{48}=CR^{49}$; suitably, R^{45} is hydrogen or C_{1-6}alkyl; suitably, R^{46} and R^{47} are independently hydrogen or C_{1-6}alkyl; suitably, J is oxygen, $CR^{50}R^{51}$, or NR^{52}, wherein suitably, R^{50}, R^{51} and R^{52} are independently hydrogen or C_{1-6}alkyl, or J is a group $S(O)_m$ wherein m is 0, 1 or 2; and suitably, i is an integer from 1 to 3, and j is an integer from 1-3. Preferably, the point of attachment of group (b) is para to substituent J.

Suitably, when E is group (c), suitably, M is oxygen, $S(O)_p$, $CR^{58}=CR^{59}$, C=C ,or $CR^{58}R^{59}$, wherein p is 0, 1 or 2, and R^{58} and R^{59} are independently hydrogen or C_{1-6}alkyl, or suitably, M is NR^{60} wherein R^{60} is hydrogen or alkyl; suitably, R^{53} and R^{54} are independently hydrogen or C_{1-6}alkyl; suitably, R^{55} is hydrogen, C_{1-6}alkyl, CO_2R^{61}, $NHCO_2R^{62}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{61} is hydrogen or C_{1-6}alkyl, and R^{62} is C_{1-6}alkyl; suitably, R^{56} is hydrogen, or together with R^{30} forms a group –Q-, wherein Q is $CR^{63}=CR^{64}$, $CR^{63}=CR^{64}CR^{63}R^{64}$, or $(CR^{63}R^{64})q$, wherein q is 2 or 3, and suitably, R^{63} and R^{64} are independently hydrogen or C_{1-6}alkyl; suitably, R^{57} is selected from a group of formula (d) or (e); suitably, n is 0, 1, 2 or 3, o is an integer from 1-2, and u is 0, 1, 2 or 3.

Suitably, when E is group (f), R^{66} and R^{67} are independently hydrogen or C_{1-6}alkyl; suitably, R^{68} and R^{69} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur; suitably, T is $-(CR^{70}R^{71})_w$- or $-O(CR^{70}R^{71})_x$-, wherein R^{70} and R^{71} are independently hydrogen or C_{1-6}alkyl, wherein w is 2 or 3, and x is 1, 2 or 3; suitably, W is oxygen, $S(O)_y$, wherein y is 0, 1 or 2, or W is NR^{72}, wherein R^{72} is hydrogen or C_{1-6}alkyl, or W is $CR^{73}=CR^{74}$, C=C, or $CR^{73}R^{74}$, wherein R^{73} and R^{74} are independently hydrogen or C_{1-6}alkyl; and suitably, v is an integer from 1-

4.

Suitably, when E is group (g), R^{75} is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy, or R^{75} and R^{30} taken together from a group -X-, wherein X is $(CR^{78}R^{79})_{aa}$, wherein aa is 2, 3 or 4, and R^{78} and R^{79} are independently hydrogen or C_{1-6}alkyl, or X is $(CR^{78}R^{79})_{ab}$-Y, wherein ab is 0, 1, 2 or 3, and Y is oxygen, sulfur or $CR^{78}=CR^{79}$; suitably, R^{76} is hydrogen, C_{1-6}alkyl, CO_2R^{80}, $NHCO_2R^{81}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{80} is hydrogen or C_{1-6}alkyl, and R^{81} is C_{1-6}alkyl; suitably, R^{77} is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, or R^{77} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom, and optionally, a further heteroatom selected from oxygen, nitrogen or sulfur; and suitably, z is an integer from 1-2.

Suitably, when E is group (h), R^{82} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halogen, or R^{82} together with R^{30} form a group -AA-, wherein AA is $(CR^{87}R^{88})$ad, wherein ad is 1, 2 or 3, and R^{87} and R^{88} are independently hydrogen or C_{1-6}alkyl, or AA is $(CR^{87}CR^{88})_{ae}$-AB, wherein ae is 0, 1 or 2, and AB is oxygen, sulfur, $CR^{87}=CR^{88}$, $CR^{87}=N$, $CR^{87}NR^{88}$ or N=N; suitably, R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl; suitably, R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur; suitably, Z is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur; and suitably ac is 0-4.

Suitably, when E is group (i), R^{89} is hydrogen or C_{1-6}alkyl or R^{89} and R^{30} together form a group -AD- wherein AD is $(CR^{94}R^{95})$ah wherein ah is 2, 3 or 4 and R^{94} and R^{95} are independently hydrogen or C_{1-6}alkyl or AD is $(CR^{94}R^{95})_{ai}$-AE wherein ai is 0, 1, 2 or 3 and AE is oxygen, sulfur or $CR^{94}=CR^{95}$; suitably, R^{90} and R^{91} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur; suitably, R^{92} and R^{93} are independently hydrogen or C_{1-6}alkyl; suitably, AC is oxygen, $CR^{96}R^{97}$ or NR^{98} wherein R^{96}, R^{97} and R^{98} are independently hydrogen or C_{1-6}alkyl or AC is a group S(O)aj wherein aj is 0, 1 or 2; suitably, af is an integer from 1-3, ag is an integer from 1-4, and ah is 0-4.

Preferably, A' is phenyl, R^1 is one or more of C_{1-6}alkyl, $(CH_2)_aNR^2COR^4$, CF_3, C_{1-6}alkoxy, or halogen, D' is a bond, E' and G' together are $NC(R^{26})_2$, R is hydrogen, J' is CO, L' is NR^{30}, and E is group (a), (b), (c), (f), (g), (h), or (i).

More preferably, A' is phenyl, R^1 is one or more of C_{1-6}alkyl, CF_3, or halogen, D' is a bond, E' and G' together are NCH_2, R is hydrogen, J' is CO, L' is NH, and E is group (a), (b), (c), (f), (g), (h), or (i). More preferably, when E is group (a), L' is attached to group (a) meta to B-$(CR^{31}R^{32})_d$-$NR^{34}R^{35}$ and para to $(R^{33})_e$, wherein B is oxygen or $CR^{39}R^{40}$, R^{31} and R^{32} are hydrogen, R^{33} is methoxy or iodo, R^{34} and R^{35} are independently C_{3-6}alkyl, or R^{34} and R^{35} taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring optionally substituted with one or more of C_{1-6}alkyl, R^{36} is hydrogen, d is 2 or 3, and e is 1. Most preferably, when E is group (b), L' is attached to group (b) para to J, J is oxygen, R^{44} is hydrogen, R^{46} and R^{47} are hydrogen, R^{45} is C_{3-6}alkyl, i is 2 and j is 1.

Most preferably, A' is phenyl, R^1 is two methyl or chloro groups substituted in the 2,3-positions, D' is a bond, E' and G' together are NCH_2, R is hydrogen, J' is CO, L' is NH, and E is group (a) or (b). Most preferably, when E is group (a), L' is attached to group (a) meta to B-$(CR^{31}R^{32})_d$-$NR^{34}R^{35}$ and para to $(R^{33})_e$, wherein B is oxygen or CH_2, R^{31} and R^{32} are hydrogen, R^{33} is methoxy, R^{34} and R^{35} are independently isopropyl, tert-butyl, or R^{34} and R^{35} taken together with the nitrogen to which they are attached are 1-(2,2,4,4-tetramethylpiperidinyl), R^{36} is hydrogen, d is 2 or 3, and e is 1. Most preferably, when E is group (b), L' is attached to group (b) para to J, J is oxygen, R^{44} is hydrogen, R^{46} and R^{47} are hydrogen, R^{45} is isopropyl, i is 2 and j is 1.

The term "C_{1-6}alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 7 carbon atoms which may be mono- or bicyclo- fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 6 carbon atoms, unless the length is limited thereto, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one double bond between two of the carbon atoms in the ring, including but not limited to cyclopentenyl, cyclohexenyl, and the like.

The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 8 carbon atoms, unless the chain length is limited thereto, wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1- propylene, 2-propylene, and the like.

The term "aryl" is used herein at all occurrences to mean 6-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthyl, biphenyl, phenanthryl, anthracenyl, and the like.

The term "heteroaryl" is used herein at all occurrences to mean a 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, which ring or ring systems contain 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, including, but not limited to, indolyl, benzofuranyl, thianaphthenyl, quinolyl, isoquinolyl, pyrrolyl, furanyl, thienyl, pyridyl, and the like.

The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as defined above, which is connected to an alkyl moiety as defined above, for example, benzyl or phenethyl, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n- propoxy, isopropoxy, and the like.

The term "oxo" is used herein at all occurrences to mean a double bonded oxygen atom attached to a chemical moiety as a substituent.

The terms "hydroxyC_{1-6}alkyl" and "hydroxyalkyl" are used herein interchangeably to mean an hydroxyl group bonded to a C_{1-6}alkyl group as defined above, including, but not limited to methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, and the like.

The term "C_{1-4}alkoxyalkyl" is used herein at all occurrences to mean a C_{1-4}alkoxy group as defined above bonded to an alkyl group as defined above, such as an ether, e.g., CH_3-CH_2-O-CH_2-CH_2-CH_3.

The term "hydroxyC_{1-6}alkoxy" is used herein at all occurrences to mean an hydroxyl group bonded to an alkoxy group as defined above, e.g., HO-CH_2-CH(OH)CH_3.

The term "C_{1-6}alkoxyC_{1-6}alkoxy" is used herein at all occurrences to mean an alkoxy group as defined above, substituted with an alkoxy group as defined above.

The term "acyloxy" is used herein at all occurrences to mean a moiety –O-C(O)-R, wherein R is hydrogen or C_{1-6}alkyl.

The term " C_{1-4}alkanoyl " is used herein at all occurrences to mean a C(O)C_{1-4}alkyl group wherein the alkyl portion is as defined above.

The term "heteroatom" is used herein at all occurrences to mean an oxygen atom, a sulfur atom or a nitrogen atom. It will be recognized that when the heteroatom is nitrogen, it may form an NR_aR_b moiety, wherein R_a and R_b are, independently, hydrogen or C_1 to C_6 alkyl, or together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6- or 7-membered ring, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, pyridine, and the like. It will be recognized that the saturated or unsaturated 5-, 6- or 7-membered ring may optionally have one or more additional heteroatoms in the ring.

The term "heterocyclic" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 5-10-membered ring system (unless the cyclic ring system is otherwise limited) in which one or more rings contain one or more heteroatoms, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, and the like.

The term "optionally substituted" is used herein at all occurrences to mean an optionally substituted 5- to 7-membered heterocyclic ring wherein the optional substituents are one or more of C_{1-6}alkyl.

The term "CCR5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by CCR5.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

Among the preferred compounds of the invention are the following compounds:

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenyl-1,2,3,6-tetrahydropyridine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenylpiperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methylphenyl)piperazine-1-carboxamide;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-acetamido-methylphenyl) piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-trifluoromethylphenyl)piperazine-1-carboxamide;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methoxyphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,6-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dichlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-(3-methylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-methoxyphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,4-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-phenylpiperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dihydro-2(1H)-quinolinone-6-yl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,5-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-cyanophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-ethoxycarbonylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-ethoxycarbonylphenyl)piperazine-1-carboxamide; and

N-[2,3-dihydro-1'-isopropyl-spiro[benzofuran-5-yl-3,4'-piperidine]]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide.

Among the more preferred compounds of the invention are the following compounds:

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide;and

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dichlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,4-dimethylphenyl)piperazine-1-carboxamide; and

N-[2,3-dihydro-1'-isopropyl-spiro[benzofuran-5-yl-3,4'-piperidine]]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an amount sufficient to treat COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, ("CCR5-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional

procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CCR5 mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more

acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other

ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans, which comprises administering to such mammal an effective amount of a CCR5 receptor modulator, in particular, a compound as depicted in formula (I).

By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of

administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods of Preparation

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

For example, compounds of formula (I) are prepared by treating a suitably substituted aniline with triphoshene followed by treatment with a suitably substituted 4-(phenyl)piperazine, 4-(phenyl)piperidine, 4-phenyl-2,3,4,6-tetrahydropyrdine, etc.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group of formula (a) are prepared according to the methods of international application publication number WO 95/15954, published 15 June 1995, international application publication number WO 95/17398, published 29 June 1995, international application publication number WO 95/26328, published 5 October 1995, and international application publication number WO 96/06079, published 29 February 1996.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (b) are prepared according to the methods of international application publication number WO 95/11934, published 25 April 1995, and WO 95/19477, published 27 June 1995. Four other applications relate to the spiro compounds WO 97/17350 published 15 May 1997; WO 97/34900 published 25 September 1997; WO 97/34901 published 25 September 1997; WO 97/35862 published 2 October 1997.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (c) are prepared according to the methods of international application publication number WO 95/30675, published 16 November 1995.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (f) are prepared according to the methods of international application publication number WO 95/17401, published 29 June 1995.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (g) are prepared according to the methods of international application publication number WO 96/31508 published 10 October 1996.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (h) are prepared according to the methods of international application publication number WO 95/32967, published 7 December 1995 and WO 97/07120, published 27 February 1997.WO 97/07120, published 27 February 1997.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (i) are prepared according to the methods of international application publication number WO 97/19070 published 29 May 1997.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In the Examples, mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.

EXAMPLES

Example 1

Preparation of N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenyl-1,2,3,6-tetrahydropyridine-1-carboxamide

A solution of triphosgene (0.23 g, 0.77 mmol) in dichloromethane (25 mL) was stirred in an ice bath and treated with a solution of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (0.5 g, 2.6 mmol) and triethylamine (1 g, 10.2 mmol) in dichloromethane added dropwise. The ice bath was removed and the mixture was stirred for 30 min, treated with 3-(2-diisopropylamino)ethoxy-4-methoxyaniline (WO 95/15954)(0.68 g, 2.55 mmol), and stirred for 16 h. The mixture was diluted with dichloromethane (50 mL), extracted with 5% sodium carbonate, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (silica gel, 8% methanol/dichloromethane saturated with ammonia) to give the title compound. MS(ES) m/e 452.0 $[M+H]^+$.

Example 2

Preparation of N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dimethylphenyl) piperazine-1-carboxamide;

Triphosgene (74 mg, 0.25 mmol) was added to a solution of 3-(2-

diisopropylamino)ethoxy-4-methoxyaniline (WO 95/15954)(200 mg, 0.75 mmol) and dichloromethane (3 mL) and maintained at RT for 30 min. Triethylamine (0.30 g, 0.42 mL, 3.0 mmol) was added and the resulting mixture was stirred for 1 h, treated with 1-(2,3-dimethylphenyl)piperazine (0.11 g, 0.60 mmol), and the mixture stirred at RT for 16 h. The mixture was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, 20:1:0.04 dichloromethane:methanol:triethylamine) to give 205 mg (70%) of the title compound as an off-white powder. MS(ES) m/e 483.1 $[M+H]^+$.

Examples 3-13

Following the procedure of Example 2, except substituting phenylpiperazine, 2-methylphenylpiperazine, 2-(acetamidomethyl)phenyl-piperazine(GB 2309458), 3-(trifluoromethyl)phenylpiperazine, 2-methoxyphenylpiperazine, 2-, 3- and 4-chlorophenylpiperazines, 2,6-dimethylphenylpiperazine, 2,3-dichlorophenylpiperazine and 3,4-dichlorophenylpiperazine for 2,3-dimethylphenylpiperazine, gave the following compounds:

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenylpiperazine-1-carboxamide: MS(ES) m/e 454. 9 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methylphenyl)piperazine-1-carboxamide: MS(ES) m/e 469.1 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-acetamido-methylphenyl) piperazine-1-carboxamide: MS(ES) m/e 525.9 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-trifluoromethylphenyl)piperazine-1-carboxamide: MS(ES) m/e 522.8 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methoxyphenyl)piperazine-1-carboxamide: MS(ES) m/e 485.0 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-chlorophenyl)piperazine-1-carboxamide: MS(ES) m/e 488.9 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-chlorophenyl)piperazine-1-carboxamide: MS(ES) m/e 488.8 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-chlorophenyl)piperazine-1-carboxamide: MS(ES) m/e 488.8 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,6-dimethylphenyl)piperazine-1-carboxamide: MS(ES) m/e 483.1 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dichlorophenyl)piperazine-1-carboxamide: MS(ES) m/e 522.9 $[M+H]^+$;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dichlorophenyl)piperazine-1-carboxamide: MS(ES) m/e 522.7 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-(3-methylphenyl)piperazine-1-carboxamide: MS(ES) m/e 483.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-methoxyphenyl)piperazine-1-carboxamide: MS(ES) m/e 499.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,4-dimethylphenyl)piperazine-1-carboxamide: MS(ES) m/e 483.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-phenylpiperazine-1-carboxamide: MS(ES) m/e 469.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dihydro-2(1H)-quinolinone-6-yl)piperazine-1-carboxamide: MS(ES) m/e 524.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,5-dimethylphenyl)piperazine-1-carboxamide: MS(ES) m/e 483.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-cyanophenyl)piperazine-1-carboxamide: MS(ES) m/e 480.2 $[M+H]^+$;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-ethoxycarbonylphenyl)piperazine-1-carboxamide: MS(ES) m/e 527.2 $[M+H]^+$; and

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-ethoxycarbonylphenyl)piperazine-1-carboxamide: MS(ES) m/e 527.2 $[M+H]^+$.

Example 23

Preparation of 1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

a) 5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of 1'-methyl-5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine] (WO 96/11934) (3 g, 12 mmol) and diisopropylethylamine (2.5 g, 19 mmol) in 1,2-dichloroethane (80 mL) was treated with 1-chloroethyl chloroformate (2.3 g, 16 mmol) at RT, stirred for 1 h, and heated to reflux for 20 min. The mixture was cooled, concentrated *in vacuo*, and the residue was dissolved in methanol and heated to reflux for 2 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (250 mL) and 5% sodium bicarbonate (50 mL). The organic phase was washed with 5% sodium bicarbonate (50 mL) and the combined aqueous phase was extracted with dichloromethane (2 X 50 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to afford the title compound

(2. 65 g).

b) 1'-(tert-butoxycarbonyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 2(a) (2.65 g, 1.13 mmol) in tetrahydrofuran (300 mL) was treated with di-tert-butyl dicarbonate (2.6 g, 12 mmol) and stirred at RT for 16 h. The mixture was concentrated *in vacuo* and the residue was crystallized from methanol to afford the title compound (2.1 g).

c) 5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 2(b)(2.1 g, 6.3 mmol) in dichloromethane (50 mL) and trifluoroacetic acid (10 mL) was kept at RT for 5 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (300 mL) and 5% sodium bicarbonate. The organic phase was washed with 5% sodium bicarbonate and the combined aqueous washes were extracted with dichloromethane. The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (1.45 g). MS(ES) m/e 235.1 $[+H]^+$.

d) 1'-(1-methylethyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A mixture of the compound of Preparation 2(c) (1.45 g, 6.2 mmol), powdered potassium carbonate (0.86 g, 6.2 mmol) and dimethylformamide (50 mL) containing 2-iodopropane (1.1 g, 6.4 mmol) was stirred and heated to 50°C for 4 h, treated with 2-iodopropane (0.17 g, 1 mmol) at 50°C for 90 min, and treated with 2-iodopropane (0.1 g, 1 mmol) at 50°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200 mL) and water (20 mL). The organic phase was washed, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica gel, 5% methanol:dichloromethane) to give the title compound (0.85 g).

e) 1'-(1-methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

A solution of the compound of Preparation 2(d) (0.78 g, 2.8 mmol) in methanol (250 mL) containing 10% palladium-on-carbon (0.375 g) was shaken in a hydrogen atmosphere (40 psi) for 40 min, filtered, and concentrated *in vacuo* to afford the title compound (0.6 g).

Example 24

Following the procedure of Example 2, except substituting 1'-(1-methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine for 3-(2-diisopropylamino)ethoxy-4-methoxyaniline, gave the following compound:

N-[2,3-dihydro-1'-isopropyl-spiro[benzofuran-5-yl-3,4'-piperidine]]-4-(2,3-

dimethylphenyl)piperazine-1-carboxamide: MS(ES) m/e 463.1 $[M+H]^+$.

Biological Data:

CCR5 Receptor Binding Assay

CHO cell membranes (0.25 x10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition

of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists).

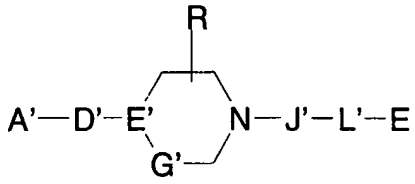
The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 μM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators of the CCR5 receptor and which bind thereto with an IC_{50} value in the range of 0.0001 to 100 μM.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating a CCR5-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula I

in which:

the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl or is optionally present as the N-oxide;

A' is aryl, heteroaryl, or tetrahydronaphthyl, optionally substituted with one or more of R^1;

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, CH_2CF_3, aryl, aralkyl, $(CH_2)_aNR^2R^3$, $(CH_2)_aNR^2COR^4$, $(CH_2)_aNR^2CO_2R^5$, $(CH_2)_aNR^2SO_2R^6$, $(CH_2)_aCONR^7R^8$, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^9$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, COR^{12}, $CONR^7R^8$, $CONR^7(CH_2)_cOC_{1-4}$alkyl, $CONR^7(CH_2)_aCO_2R^{13}$, $CONHNR^{14}R^{15}$, $CONR^7SO_2R^{16}$, CO_2R^{17}, cyano, trifluoromethyl, NR^2R^3, NR^2COR^4, $NR^{18}CO(CH_2)_aNR^{18}R^{19}$, $NR^{18}CONR^{18}R^{19}$, $NR^2CO_2R^5$, $NR^2SO_2R^6$, $N=CNR^{18}NR^{18}R^{19}$, nitro, hydroxy, C_{1-6}alkoxy, OCF_3, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{20}R^{21}$, SR^{22}, SOR^{23}, SO_2R^{23}, $SO_2NR^{20}R^{21}$ or halogen, or R^1 is a 5- to 7-membered ring containing 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, optionally substituted with hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, (C_{1-6}alkyl)C_{1-6}alkyl, $CONR^7R^8$, CO_2R^{17}, cyano, aryl, trifluoromethyl, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen;

a is 1, 2, 3 or 4;

b is 0, 1, 2 or 3;

c is 1, 2 or 3;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl, or R^2 and R^3 together with the nitrogen to which they are attached, form a 5- to 6-membered heterocyclic ring which ring may be optionally substituted by an oxo group, or, when there are

6 ring members, the ring may optionally contain one oxygen or one sulfur atom;

R^4 is hydrogen, C_{1-6}alkyl or C_{1-4}alkoxyalkyl, or, when R^1 is NR^2COR^4, R^4 is $(CH_2)_{1-3}$ and forms a ring with A';

R^5 is C_{1-6}alkyl;

R^6 is C_{1-6}alkyl or phenyl;

R^7 and R^8 are independently hydrogen or C_{1-6}alkyl, or R^7 and R^8 together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring, wherein when there are 6 ring members, the ring may optionally contain one oxygen or one sulfur atom;

R^9 is C_{1-4}alkyl, optionally substituted by a C_{1-6}alkoxy;

R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^{12} is hydrogen or C_{1-6}alkyl;

R^{13} is hydrogen or C_{1-6}alkyl;

R^{14} and R^{15} are independently hydrogen or C_{1-6}alkyl;

R^{16} is hydrogen or C_{1-6}alkyl;

R^{17} is hydrogen or C_{1-6}alkyl optionally substituted with one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or NR^2R^3;

R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl;

R^{20} and R^{21} are independently hydrogen or C_{1-6}alkyl, or R^{20} and R^{21} together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain in the ring one oxygen or one sulfur atom.

R^{22} is hydrogen or C_{1-6}alkyl;

R^{23} is C_{1-6}alkyl;

D' is either a bond or represents $[C(R^{24})_2]_a$', $[C(R^{24})_2]_a$'CO, CO, $CO[C(R^{24})_2]_a$', $O[C(R^{24})_2]_a$', $S[C(R^{24})_2]_a$', $O[C(R^{24})_2]_a$'CO, $[C(R^{24})_2]_c$'OCO, $NR^{25}[C(R^{24})_2]_a$', $NR^{25}[C(R^{24})_2]_a$'CO, $[C(R^{24})_2]_c$'$NR^{25}CO$, $NR^{25}CO[C(R^{24})_2]_a$', $NR^{25}SO_2[C(R^{24})_2]_a$', $[C(R^{24})_2]_c$'$NR^{25}SO_2$, CR^{24}=$CR^{24}CO$, C≡CCO, $(C(R^{24})_2)_c$'SO_2, $SO_2[C(R^{24})_2]_a$', $NR^{25}[C(R^{24})_2]_a$'SO_2, $NR^{25}SO_2[C(R^{24})_2]_a$'$SO_2$, $O[C(R^{24})_2]_a$'SO_2, $SO_2NR^{25}[C(R^{24})_2]_{1-2}$, $[C(R^{24})_2]_b$'$COO[C(R^{24})_2]_2$, $[C(R^{24})_2]_b$'$CONR^{25}[C(R^{24})_2]_{1-2}$; and when E' and G' together are CR^{27}-$C(R^{26})_2$, then D' may further be O, NR^{25}, $CONR^{25}$, SO_2NR^{25}, $OCONR^{25}$, $NR^{25}COO$, $NR^{25}CONR^{25}$, $[C(R^{24})_2]_a$'$NR^{25}[C(R^{24})_2]_b$', $[C(R^{24})_2]_a$'$O[C(R^{24})_2]_b$', $CO[C(R^{24})_2]_a$'NR^{25}, $NR^{25}[C(R^{24})_2]_a$'O, $NR^{25}[C(R^{24})_2]_a$'NR^{25}, $O[C(R^{24})_2)]_a$'NR^{25}, $O[C(R^{24})_2]_a$'O, $CO[C(R^{24})_2]_a$'O, $SO_2[C(R^{24})_2]_a$'NR^{25}, $SO_2[C(R^{24})_2]_a$'O, $[C(R^{24})_2]_a$'SO_2NR^{25},

$[C(R^{24})_2]_a$-$CONR^{25}$, $O[C(R^{24})_2]_a$-SO_2NR^{25}, $O[C(R^{24})_2]_a$-$CONR^{25}$, $NR^{25}[C(R^{24})_2]_a$-SO_2NR^{25}, $NR^{25}[C(R^{24})_2]_a$-$CONR^{25}$, $NR^{25}CO[C(R^{24})_2]_a$-NR^{25}, $NR^{25}SO_2[C(R^{24})_2]_a$-$NR^{25}$, $(C(R^{24})_2)_a$-$S(C(R^{24})_2)_b$-, COO, $CR^{24}OH$, $C(R^{24})_a$-$CR^{24}OH$; and when E' and G' together are CR^{27}-$C(R^{26})_2$ or $C{=}CR^{26}$, D' may further be $CR^{24}{=}CR^{24}$ or C≡C; and a' is 1-6, b' is 0-1, c' is 0-2;

R^{24} is hydrogen or C_{1-6}alkyl;

R^{25} is hydrogen or C_{1-6}alkyl;

E' and G' together are $NC(R^{26})_2$, $NC(R^{26})_2C(R^{26})_2$, $CR^{27}C(R^{26})_2$ or $C{=}CR^{26}$;

R^{26} is hydrogen or C_{1-6}alkyl;

R^{27} is hydrogen, OR^{28}, NHR^{28}, CN, NO_2, R^{28}, SR^{29}, COR^{29}, $CHOHR^{29}$, CO_2R^{29}, $NHCOR^{29}$, $NHCO_2R^{29}$, $NHSO_2R^{29}$, or $OCONHR^{29}$;

R^{28} is hydrogen, C_{1-5}alkyl, aryl or aralkyl;

R^{29} is C_{1-5}alkyl, aryl or aralkyl;

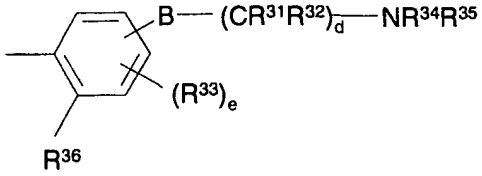
R is one or more of hydrogen or C_{1-6}alkyl, or R is oxo;

J' is CO or SO_2;

L' is NR^{30}, O or $C(R^{30})_2$;

R^{30} is hydrogen or C_{1-6}alkyl;

E represents group (a):



(a);

in which

R^{31} and R^{32} are independently hydrogen or C_{1-6}alkyl;

R^{33} is hydrogen, C_{1-6}alkyl, CO_2R^{37}, $NHCO_2R^{38}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{37} is hydrogen or C_{1-6}alkyl and R^{38} is C_{1-6}alkyl;

d is 1 to 4;

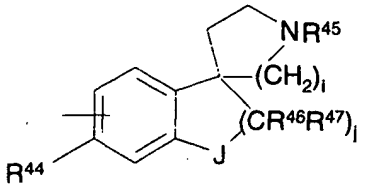
e is 1 or 2;

R^{34} and R^{35} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

B is oxygen, $S(O)_f$, $CR^{39}{=}CR^{40}$, C=C, or $CR^{39}R^{40}$ wherein R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl, and wherein f is 0, 1 or 2, or B is NR^{41} wherein R^{41} is hydrogen, C_{1-6}alkyl or phenylC_{1-6}alkyl; and

R^{36} is hydrogen or R^{36} taken together with R^{30} forms a group D, wherein D is $(CR^{42}R^{43})_g$, wherein g is 2, 3 or 4, and R^{42} and R^{43} are independently hydrogen or C_{1-6}alkyl, or D is $(CR^{42}R^{43})_h$-G wherein h is 0, 1, 2 or 3, and G is oxygen, sulfur or $CR^{42}=CR^{43}$;

alternatively, E represents group (b):



(b);

in which:

R^{44} is hydrogen or C_{1-6}alkyl, or R^{44} and R^{30} together form a group -K-, wherein K is $(CR^{48}R^{49})_k$, wherein k is 2, 3, or 4, and R^{48} and R^{49} are independently hydrogen or C_{1-6}alkyl, or K is $(CR^{48}R^{49})_l$ –L, wherein l is 0, 1, 2, or 3, and L is oxygen, sulfur or $CR^{48}=CR^{49}$;

R^{45} is hydrogen or C_{1-6}alkyl;

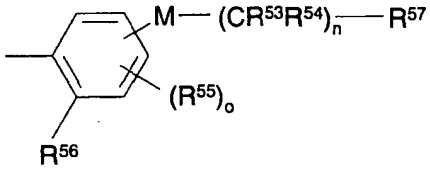
R^{46} and R^{47} are independently hydrogen or C_{1-6}alkyl;

J is oxygen, $CR^{50}R^{51}$, or NR^{52}, wherein R^{50}, R^{51} and R^{52} are independently hydrogen or C_{1-6}alkyl, or J is a group $S(O)_m$ wherein m is 0, 1 or 2;

i is 1, 2 or 3; and

j is 1, 2 or 3;

alternatively, E represents group (c):



(c);

in which:

M is oxygen, $S(O)_p$, $CR^{58}=CR^{59}$, C=C, or $CR^{58}R^{59}$, wherein p is 0, 1 or 2, and R^{58} and R^{59} are independently hydrogen or C_{1-6}alkyl, or M is NR^{60} wherein R^{60} is hydrogen or alkyl;

R^{53} and R^{54} are independently hydrogen or C_{1-6}alkyl;

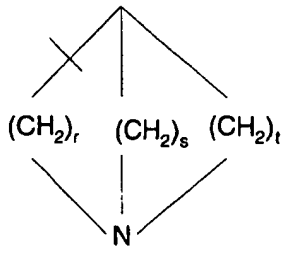
R^{55} is hydrogen, C_{1-6}alkyl, CO_2R^{61}, $NHCO_2R^{62}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{61} is hydrogen or C_{1-6}alkyl, and R^{62} is C_{1-6}alkyl;

R^{56} is hydrogen, or together with R^{30} forms a group –Q-, wherein Q is $CR^{63}=CR^{64}$, $CR^{63}=CR^{64}CR^{63}R^{64}$, or $(CR^{63}R^{64})q$, wherein q is 2 or 3, and R^{63} and R^{64} are independently hydrogen or C_{1-6}alkyl;

n is 0, 1, 2 or 3;

o is 1 or 2; and

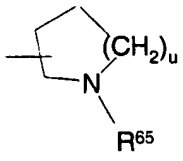
R^{57} is a group of formula (d):



(d)

wherein r, s and t are independently integers having the value 1, 2 or 3;

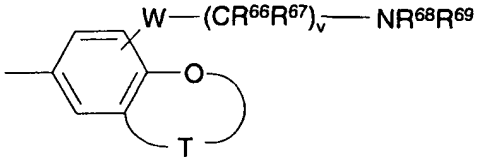
or R^{57} is a group of formula (e), which may be optionally substituted by one or more of C_{1-6}alkyl:



(e)

wherein u is 0,1, 2 or 3 and R^{65} is hydrogen or C_{1-6}alkyl;

alternatively, E represents group (f):



(f);

in which:

R^{66} and R^{67} are independently hydrogen or C_{1-6}alkyl;

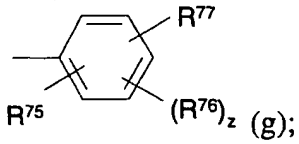
R^{68} and R^{69} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

T is $-(CR^{70}R^{71})_w-$ or $-O(CR^{70}R^{71})_x-$, wherein R^{70} and R^{71} are independently hydrogen or C_{1-6}alkyl, wherein w is 2 or 3, and x is 1, 2 or 3;

v is 1 to 4; and

W is oxygen, $S(O)_y$, wherein y is 0, 1 or 2, or W is NR^{72}, wherein R^{72} is hydrogen or C_{1-6}alkyl, or W is $CR^{73}=CR^{74}$ or $CR^{73}R^{74}$, wherein R^{73} and R^{74} are independently hydrogen or C_{1-6}alkyl;

alternatively, E represents group (g):



(g);

in which:

R^{75} is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy, or R^{75} and

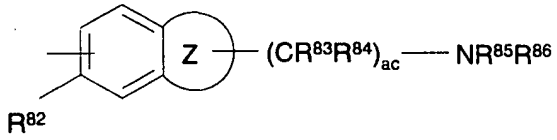
R^{30} taken together from a group -X-, wherein X is $(CR^{78}R^{79})_{aa}$, wherein aa is 2, 3 or 4, and R^{78} and R^{79} are independently hydrogen or C_{1-6}alkyl, or X is $(CR^{78}R^{79})_{ab}$-Y, wherein ab is 0, 1, 2 or 3, and Y is oxygen, sulfur or $CR^{78}=CR^{79}$;

R^{76} is hydrogen, C_{1-6}alkyl, CO_2R^{80}, $NHCO_2R^{81}$, hydroxy, C_{1-6}alkoxy or halogen, wherein R^{80} is hydrogen or C_{1-6}alkyl, and R^{81} is C_{1-6}alkyl;

z is 1 or 2; and

R^{77} is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, or R^{77} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom, and optionally, a further heteroatom selected from oxygen, nitrogen or sulfur;

alternatively, E represents group (h):



(h);

in which:

R^{82} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halogen, or R^{82} together with R^{30} form a group -AA-, wherein AA is $(CR^{87}R^{88})$ad, wherein ad is 1, 2 or 3, and R^{87} and R^{88} are independently hydrogen or C_{1-6}alkyl, or AA is $(CR^{87}CR^{88})_{ae}$-AB, wherein ae is 0, 1 or 2, and AB is oxygen, sulfur, $CR^{87}=CR^{88}$, $CR^{87}=N$, $CR^{87}NR^{88}$ or N=N;

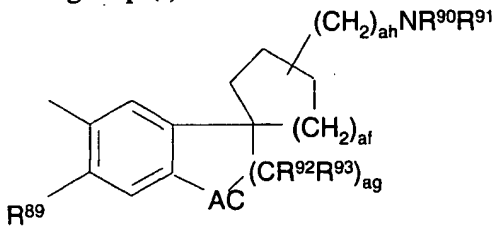
R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl;

R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

ac is 0 to 4; and

Z is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

alternatively, E is group (i):



(i);

in which:

R^{89} is hydrogen or C_{1-6}alkyl or R^{89} and R^{30} together form a group -AD- wherein AD is $(CR^{94}R^{95})$ah wherein ah is 2, 3 or 4 and R^{94} and R^{95} are independently hydrogen or C_{1-6}alkyl or AD is $(CR^{94}R^{95})_{ai}$-AE wherein ai is 0, 1, 2 or 3 and AE is oxygen, sulfur or $CR^{94}=CR^{95}$;

R^{90} and R^{91} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one to two heteroatoms selected from oxygen, nitrogen or sulfur;

R^{92} and R^{93} are independently hydrogen or C_{1-6}alkyl;

AC is oxygen, $CR^{96}R^{97}$ or NR^{98} wherein R^{96}, R^{97} and R^{98} are independently hydrogen or C_{1-6}alkyl or AC is a group S(O)aj wherein aj is 0, 1 or 2;

af is 1, 2 or 3;

ag is 1, 2, 3, or 4; and

ah is 0, 1, 2, 3 or 4.

2. The method as claimed in claim 1 wherein the compound of formula (I) is a compound selected from:

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenyl-1,2,3,6-tetrahydropyridine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenylpiperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methylphenyl)piperazine-1-carboxamide;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-acetamido-methylphenyl) piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-trifluoromethylphenyl)piperazine-1-carboxamide;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methoxyphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,6-

dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dichlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dichlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-(3-methylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-methoxyphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,4-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-phenylpiperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dihydro-2(1H)-quinolinone-6-yl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,5-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-cyanophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-ethoxycarbonylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-ethoxycarbonylphenyl)piperazine-1-carboxamide; and

N-[2,3-dihydro-1'-isopropyl-spiro[benzofuran-5-yl-3,4'-piperidine]]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide.

3. The method as claimed in claim 1, wherein the disease is selected from COPD, asthma and atopic disorders, rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection.

4. The method of claim 3, wherein the compound is selected from:

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenyl-1,2,3,6-tetrahydropyridine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-phenylpiperazine-

1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methylphenyl)piperazine-1-carboxamide;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-acetamido-methylphenyl) piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-trifluoromethylphenyl)piperazine-1-carboxamide;

N-[3-(2-diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-methoxyphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-chlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,6-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dichlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,3-dichlorophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-(3-methylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-methoxyphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2,4-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-3-methyl-4-phenylpiperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,4-dihydro-2(1H)-quinolinone-6-yl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3,5-dimethylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(3-cyanophenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(4-ethoxycarbonylphenyl)piperazine-1-carboxamide;

N-[3-(2-Diisopropylamino)ethoxy-4-methoxyphenyl]-4-(2-ethoxycarbonylphenyl)piperazine-1-carboxamide; and

N-[2,3-dihydro-1'-isopropyl-spiro[benzofuran-5-yl-3,4'-piperidine]]-4-(2,3-dimethylphenyl)piperazine-1-carboxamide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01908

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A01N 43/58

US CL :514/252.10, 252.12, 252.13, 252.18, 252.19, 252.20, 253.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252.10, 252.12, 252.13, 252.18, 252.19, 252.20, 253.01

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: COMPOUNDS, ANTIVIRAL AND ANTIINFLAMMATORY METHODS OF USE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 758 328 A1 (PIERRE FABRE MEDICAMENT) 17 July 1998 (17/07/1998) see entire patent.	1-4
A	EP 0 524 146 A1 (CIBA GEIGY AG) 20 January 1993 (20/01/1993) see entire patent.	1-4
A	BE 767846 A1 (GRUPPO LEPETIT SPA) 18 October 1971 (18/10/1971) see entire patent.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

06 APRIL 2000

Date of mailing of the international search report

26 APR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

RUSSELL TRAVERS

Telephone No. (703) 308-1235